Platform: Computational Systems Biology and Cellular Network

3249-Plat

Integrated 3D Simulation of Cardiomyocyte Revealed the Distinct Functional Characteristics between Subsarcolemmal and Interfibrillar Mitochondria

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It has been reported that two subpopulations of mitochondria exist in cardiomyocyte: subsarcolemmal mitochondria (SSM) and interfibrillar mitochondria (IFM). However, their functional characteristics have yet to be clarified, due to the experimental difficulties in differential isolation and assessment techniques. We have already developed a 3-D computational model of cardiomyocyte with subcellular structure integrating electrophysiology, metabolism, and mechanics. In this study, this model was further improved to include the intracellular gradient of oxygen and myoglobin distribution to test the hypothesis that the difference in location within the cell can introduce significant changes in mitochondrial metabolism. For this purpose, all mitochondria in the model were made to have the same membrane permeability and enzymatic activities. When compared the responses of [Ca^{2+}], TCA activity, [NADH] and mitochondrial inner membrane potential to an abrupt changes in pacing frequency (0.25 Hz to 2 Hz) between SSM and IFM, IFM reached higher plateau levels in all of these parameters. These differences seemed to be related to the intracellular gradient in [Ca^{2+}]. We also examined the effect of reduction in [O2]. Under normal condition intracellular [O2] is much higher than the half saturation concentration for oxidative phosphorylation even for the IFM located in the core region of the cell. However under limited extracellular [O2] environment, [NADH] and inner membrane potential gradually decreased in IFM compared to SSM reflecting the intracellular [O2] gradient from the cell surface to the core. Although further validations are required, the current simulation results suggested that only the difference in intracellular location can cause the different functional characteristics of mitochondrial metabolism in cardiomyocytes.

3250-Plat

Pysb: A Modeling Framework to Explore Biochemical Signaling Processes and Cell-Decisions

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Experiments often result in observations that suggest conflicting biochemical mechanisms in signaling networks. Mathematical modeling of biological systems could be used to probe knowledge derived from experimental observations. However, probing multiple mechanistic hypotheses in biological modeling often involves the instantiation of complex systems of equations that can make model revision, extension, and sharing challenging. To address these modeling barriers, we have developed a modeling framework that brings a program-based approach to biological modeling. In our approach, biological models are written as Python programs that encode biological functions as executable code. I will discuss the development and implementation of these methods to explore intracellular signaling pathway crosstalk and response to external cues in the context of programmed cell death and life/death decision processes in cancer biology will be presented. Our approach to model calibration to experimental data, extracting important knowledge from biochemical signaling networks, and developing tools to relate models to experiment will be discussed. We will also highlight how a programming language for biological modeling facilitates model tracking, sharing, and dissemination.

3251-Plat

The Evolution of Crosstalk in Signaling Networks

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The degree of crosstalk observed in signaling networks varies widely across evolution. In eukaryotes, crosstalk is widespread, with some kinases acting on hundreds of downstream targets. In bacteria, however, signaling pathways are essentially completely isolated from one another. It is currently unclear what pressures have driven the evolution of these vastly different topologies. The basic "building block" of eukaryotic signaling networks is a pair of enzymes, one that modifies a substrate (e.g. a kinase) and one that undoes this modification (e.g. a phosphatase). We recently used mathematical models to show that adding crosstalk to this type of system can increase ultrasensitivity and couple signal responses, behaviors that could yield phenotypic benefits for eukaryotic cells. In contrast, bacterial networks utilize Two-Component Signaling (TCS), in which a single enzyme (the sensor Histidine Kinase, or HK) acts as both kinase and phosphatase for its downstream Response Regulator (RR). We found that crosstalk always reduces signal response in TCS, providing an explanation for the experimental observation that engineering crosstalk into bacterial cells dramatically reduces their fitness. The pressure to maintain signaling responses is also sufficient to quantitatively explain the kinetic preference of HKs for their cognate substrates. Using our models, we characterized a set of ''near-neutral'' evolutionary pathways that would allow bacteria to minimize the impact of crosstalk as they evolve new HK-RR pairs through duplication and divergence of existing pathways. Analysis of HK sequences confirmed that most TCS pathways evolve via the trajectories we predicted. Our work thus indicates that the different topologies of eukaryotic and bacterial signaling networks likely arise from fundamental differences in the behavior of the motifs from which the networks themselves are constructed. These differences have important consequences for both the function and the evolutionary dynamics of information processing systems within cells.

3252-Plat

Computational Modeling of Biofilm Structure and Functions with Bacteria Motility Feature and Experiment Validation

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Biofilm is ubiquitous in our daily life, such as in dental plaque and sewage pipes. It is a microorganism, where bacteria stick together by secreting extracellular polymeric substances (EPS), a complex biophysical world. Biofilm is the main factor for much chronic disease, thus understanding the mechanics in biofilm development is critical for therapeutic treatment of biofilm.
In this talk, our work on computational hydrodynamic modeling of biofilm would be presented. Both kinetic approaches from bacteria collision effects, and macroscopic view of mixing free energy will been discussed. Using GPGPU, 3D numerical solver has been developed analyzing biofilm structure and functions, such as heterogeneous structure formation, antimicrobial persistent and quorum sensing features. Bacteria motility modeling in biofilm will be studied, as well, from both microscopic and macroscopic view.
Besides, our model has been validated by our collaborators' experiment results for varying biofilm persistence to antibiotics at different age and biofilm relapse after the cease of dosing. Persuasively, our model agrees quantitatively well. Hence it turns out to be an effective tool for analyzing the mechanism of biofilm formation and antimicrobial persistence, as well as therapeutic treatment of biofilm.

3253-Plat

Identifying Active Neurons from In Vivo 2-Photon Calcium Imaging of the Brain via Pixel Correlation Analysis and Region-Growing Segmentation

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Calcium imaging of neurons is a powerful tool to measure in vivo neuronal activity where one of the key challenges for calcium spike train characterization is its requirement for rapid temporal sampling to resolve fluorescent transients. However, to distinguish nearby cells that have only small differences in their firing patterns remains a challenge. Current automated image segmentation techniques which rely on the spatial analysis of image intensity, fail to accurately identify single-cell regions of interest (ROI). We present a cell parsing technique that combines a region-growing method and correlation analysis of pixel stacks to find and optimize the ROI boundaries of single cells in calcium imaging times series. While a spatio-temporal correlation function gives a signature of the calcium activity, a region-growing method gathers correlated activity into ROIs. In computer simulations of calcium imaging data sets, the algorithm was able to generate appropriate ROIs including those with irregular morphologies. The algorithm was also applied to in vivo 2-photon calcium imaging of Oregon Green BAPTA-1 in the Xenopus laevis optic tectum and retina, in both cases effectively identifying active single cell ROIs corresponding to confirmed cell boundaries. These results demonstrate that the combination of a region-growing method with correlation analysis for segmentation permits robust automated cell segmentation which has the potential to identify